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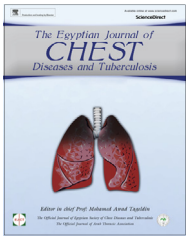

ORIGINAL ARTICLE

Serum resistin level in obstructive sleep apnea patients complicated with cardiac diseases, diabetes mellitus or renal impairment

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KEYWORDS

OSA;
Cardiac;
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Abstract *Background:* Obstructive sleep apnea (OSA) has been independently associated with cardiovascular diseases, including hypertension, coronary heart disease and heart failure. Also, it had a deleterious impact on renal function and a link to diabetes mellitus (DM) and insulin resistance. Resistin is new adipokine and may play a role in cardiac, diabetics and renal patients.

Aim of the work: The aim of this work is screening of cardiac dysfunction, DM and renal impairment in OSA patients and to study the role of resistin serum level in occurrence of these complications.

Subjects and methods: This study was carried out on 10 control persons (group I) and 143 patients with OSA (group II). The following were done to all persons: body mass index (BMI), blood pressure measurement, fasting and post prandial blood sugar levels, serum creatinine and ECG, diagnostic sleep study, echocardiogram, estimated glomerular filtration rate (eGFR) and serum resistin assay. According to the above results, group II was divided into 4 subgroups, A (33OSAS patients), B (21 OSAS patients with cardiac troubles), C (40 OSAS patients with DM) and D (13 OSAS patients with renal impairment). 36 OSAS patients were excluded from the study because they had either 2 or more of the above abnormalities (cardiac, DM and renal).

Results: There was significant increase of ESS and plasma resistin level in subgroups IIB, IIC and IID as compared group I and subgroup IIA which was significantly increased as compared to group I. There was no significant difference of BMI in subgroups IIA, IIB, IIC and IID but SaO_2 and AHI were significantly increased in subgroups IIB, IIC and IID as compared to IIA. In group II, there was a significant positive correlation between plasma resistin level and AHI, SaO_2 but there was no significant correlation between BMI and plasma resistin level.

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Conclusion: OSA patients can be complicated with cardiac diseases, DM and renal impairment through elevated resistin serum levels.

Recommendation: Effect of CPAP on resistin serum level must be evaluated in these patients.

Introduction

Obstructive sleep apnea (OSA) is a growing problem in the United States with important negative health implications. In addition to substantial morbidity as evidenced by increased health services utilization [1], reduced functional capabilities and lower quality of life [2], OSA has also been associated with increased mortality [3]. OSA has been independently associated with cardiovascular diseases, including hypertension [4], coronary heart disease, heart failure, and stroke [5]. Several mechanisms have been proposed to explain this excess cardiovascular risk among individuals with OSA, including hypoxemia-induced endothelial dysfunction, accelerated atherosclerosis, and altered cardiovascular hemodynamics. Each of these factors can have a deleterious impact on renal function so, there is a link between OSA and chronic kidney disease (CKD). Although data are limited, OSA appears to alter renal hemodynamics and function in a harmful manner [6]. Cross-sectional results from the Sleep Heart Health Study have shown a significant association between obstructive sleep apnea and chronic heart failure [7]. The prevalence of obstructive sleep apnea in a population with chronic heart failure has been shown to be as high as 30–40% [8,9]. Comorbidities, accompanying obstructive sleep apnea such as systemic hypertension and obesity [10], are also associated with the development of chronic heart failure [11]. Ciccone et al. have established that the severity and duration of obstructive sleep apnea are independent contributors for early atherosclerotic lesions, as assessed by the intima media thickness [12]. Moreover emerging data suggest that obstructive sleep apnea is not only associated with, but also contributes to the progression of cardiac remodeling in heart failure through different mechanisms. Also, OSA has a link to diabetes mellitus (DM) and insulin resistance as confirmed by Lp et al. (2002) who found that OSA subjects were more insulin resistant as indicated by their higher levels of serum insulin and insulin resistance index and concluded that apnea-hypopnea index (AHI) and minimum oxygen saturation attained during sleep are independent determinants of insulin resistance [13]. Resistin is an adipocyte-derived cytokine (adipokine) that may contribute to the development of obesity [14–16], insulin resistance [17,18] and the metabolic syndrome. More recent studies have shown the causative association between resistin and systemic inflammation [19,20], especially in the vascular endothelium [21]. From the viewpoint of inflammation, it is notable that plasma resistin concentrations increase with increasing inflammatory mediator levels predicting the severity of coronary atherosclerosis [22] also, Axelsson et al. (2006) concluded that the serum level of resistin was higher in patients with CKD [23].

Aim of the work

The aim of this work is screening of cardiac dysfunction, DM and renal impairment in OSA patients and to study the role of resistin serum level in occurrence of these complication.

Subjects and methods

This study was carried out on 143 patients with OSAS and 10 control persons in the period from January 2011 to April 2014 in Chest Department – Tanta University Hospital. Epworth Sleepiness Scale (ESS) was done to 2500 persons (non-smokers, not known to be cardiac, diabetic or renal patients). 152 persons had ESS 11 or more (9 refused to complete the study), 2348 persons had ESS > 9 (10 of them was considered as control group). All persons included in this study were divided into 2 groups, group I (10 control persons, their mean age was 53.2 ± 1.9 years) and group II (143 persons suspected to be OSAS patients, their mean age was 57.4 ± 2.8 years). The following were done to all persons:

Body mass index (BMI)

Blood pressure measurement (2 times/day for 3 successive days), fasting and post prandial blood sugar levels (patients were considered diabetics if FPG or PPG levels were ⩾126 and ⩾200 mg/dl), serum creatinine and ECG (Resting electrocardiogram was performed to detect the cardiac rhythm, presence or absence of arrhythmias and the presence of ischemia or chamber enlargement).

Diagnostic sleep study

It was conducted in the sleep laboratory unit, chest department, Tanta university hospital for at least 6 h and started at 10 pm using ResMed ApneaLink™ Plus system which has the following components:

a- ApneaLink Plus device recorder which registers patient's respirations with the nasal pressure cannula.
b- Effort sensor measures the respiratory effort.
c- Thoraco-abdominal belt.
d- Nasal cannula (Res Med soft cannula no. 70388).
e- Pulse oximeter with finger pulse sensor measuring the blood oxygen saturation and pulse rate.
f- USB cable.
g- Computer with ApneaLink Plus software installed.

Echocardiogram

Transthoracic two-dimensional (2D) echocardiography was performed using digital commercial harmonic imaging

ultrasound systems equipped with a S3 3 MHz phased-array transducer (Vivid 7, General Electrics Healthcare Systems, USA) with the patient in the left-lateral decubitus position and a raised left arm. Images were adjusted for depth, focus position, frame rate and sector size for an optimal display of the structure of interest. Images were displayed on the echocardiographic system and measurements were obtained from recordings in the parasternal LAX acoustic window directly from the 2D images. End-diastolic and end-systolic frames were identified visually by frames with the greatest and the smallest LV cavity. Dimensions were measured in the LV minor axis plane at the mitral chordae level at the tips of the papillary muscles. LVIDd and LVIDs, respectively and wall thicknesses (anteroseptal–IVSd and inferolateral–LVPWd) were measured at end-diastole(d) and end-systole(s), respectively, and were averaged over three consecutive heart cycles [24].

Estimated glomerular filtration rate (EGFR): Modification of diet in renal disease (MDRD) equation

GFR (mL/min/1.73 m^2) = $186 \times (\text{Scr} \times 0.0113) - 1.154 \times (\text{age}) - 0.203 \times (0.742$ if female) [25]. The GFR $\geqslant$ 90 mL/min/1.73 m^2 is considered to be normal if there is no clinical manifestation of renal disease [26].

Serum resistin assay

After sleep study between 8:00 am and 9:00 am on the morning, venous blood sample was obtained in the fasting state to measure resistin plasma level using performed commercially available assays or routine methods (Kit from LINCO Research, St Charles, MS) [23].

According to above results, group II was divided into 4 subgroups, A (33OSAS patients), B (21 OSAS patients with cardiac troubles), C (40 OSAS patients with DM) and D (I3 OSAS patients with renal impairment). 36 OSAS patients were excluded from the study because they had either 2 or more of the above abnormalities (cardiac, DM and renal).

Results

There was significant increase of ESS and plasma resistin level in subgroups IIB, IIC and IID as compared group I and subgroup IIA which was significantly increased as compared to group I. There was no significant difference of BMI in subgroups IIA, IIB, IIC and IID but SaO_2 and AHI were significantly increased in subgroups IIB, IIC and IID as compared to IIA. In group II, there was a significant positive correlation between plasma resistin level and AHI, SaO_2 but there was no significant correlation between BMI and plasma resistin level (Figs 1–4, Tables 1–10).

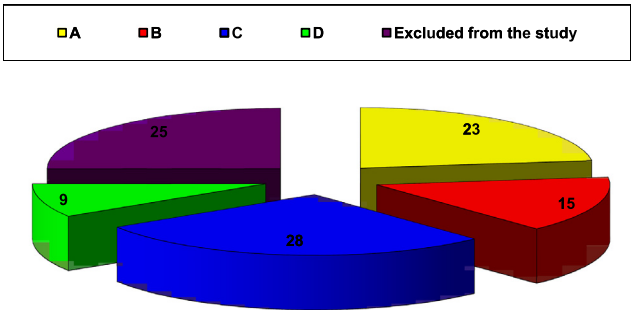

Figure 1 Percent of patients in subgroups A, B, C and D.

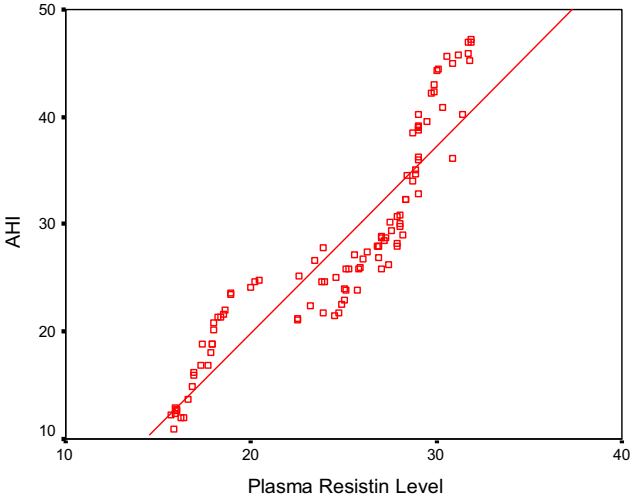

Figure 2 Correlation between plasma resistin level and AHI in group II.

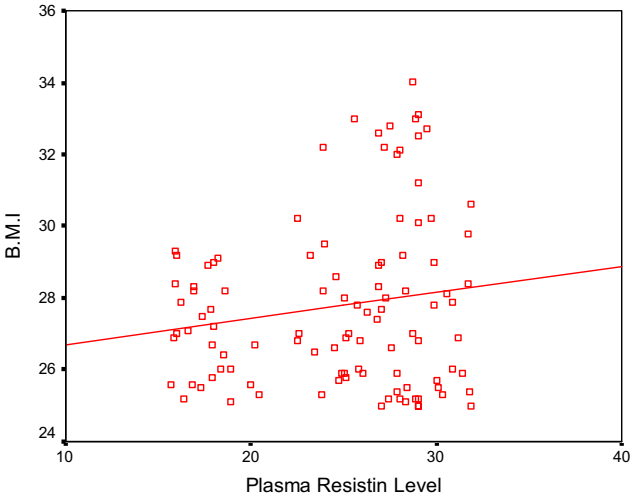

Figure 3 Correlation between plasma resistin level and BMI in group II.

Discussion

Obstructive sleep apnea (OSA) is closely related to systemic inflammation [27]. A wide variety of pro-inflammatory mediators are elevated in the circulation of patients with OSA [28,29]. Additionally, OSA patients have peripheral leukocytes which can generate larger amounts of cytokines [30,31], adhesion molecules [32] and free radicals [33]. In general however it is predominantly associated with markers of inflammation – C-reactive protein, tumor necrosis factor-α and interleukin-6, which are well accepted predictors of heart failure incidence

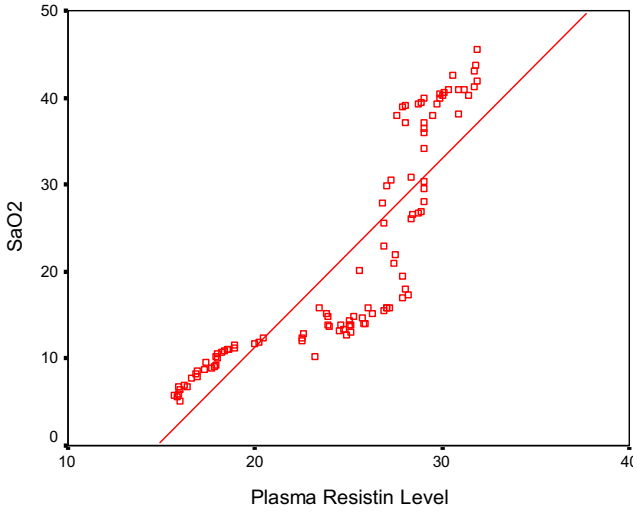

Figure 4 Correlation between plasma resistin level and SaO_2 in group II.

Table 1 Number and percent of patients in subgroups A, B, C and D.

	N (143)	Percent
A	33	23
B	21	15
C	40	28
D	13	9
Excluded from the study	36	25

Table 2 Mean and standard deviation of some echocardiographic parameters and blood pressure in subgroup IIB.

	Minimum	Maximum	Mean	Std. deviation
LVEDD	53.00	69.00	59.05	5.136
LVESD	35.00	56.00	43.73	6.606
Septal wall thickness	11.00	16.00	14.57	1.804
Posterior wall thickness	11.00	15.00	13.47	1.576
Blood pressure systolic	150.00	200.00	175.78	14.362
Blood pressure diastolic	100.00	120.00	107.63	5.619

Table 3 Clinical criteria of subgroup IIB.

		Frequency	Percent
LL edema	+ve	19	90.50
Orthopnea	+ve	19	90.50
Chest pain	+ve	19	90.50
ECG changes	IHD	11	52
	IHD + Sinus tachycardia	4	19
	IHD + Extrasystoles	5	24
	IHD + Supraventricular tachycardia	1	5

[34,35]. Lehrke et al. concluded that Inflammation is a hyper-resistinemic state in humans, and cytokine induction of resistin may contribute to insulin resistance in endotoxemia, obesity, and other inflammatory states [19]. Bokarewa et al. found that resistin accumulates in the inflamed joints of patients with rheumatoid arthritis and its levels correlate with other markers of inflammation and displays its potent pro-inflammatory properties by (1) strongly up-regulating IL-6 and TNF-alpha, (2) responding to TNF-alpha challenge, (3) enhancing its own activity by a positive feedback, and finally (4) inducing arthritis when injected into healthy mouse joints. Pro-inflammatory properties of resistin were abrogated by NF-κB inhibitor indicating the importance of NF-kappaB signaling pathway for resistin-induced inflammation and concluded that resistin is a new and important member of the cytokine family with potent regulatory functions [20]. Yamamoto et al. found that levels of resistin and IL-6 were simultaneously elevated in men with OSA compared with those in men without OSA and tended to increase with increasing disease severity, which was based on the apnea-hypopnea index (AHI) and the average oxyhemoglobin saturation during sleep. Resistin production can be enhanced by hypoxic stress during sleep in OSA patients, possibly mediating systemic inflammatory processes [36]. In contrast, Ursavas et al. concluded that no significant difference was noted in the levels of resistin in the OSA group when compared to controls and there was also no significant correlation was observed between resistin, and any polysomnographic parameters [37]. Hung et al. found that hypoxia increases the resistin expression in cultured rat vascular smooth muscle cells under hypoxia. The hypoxia-induced resistin is mediated through reactive oxygen species, ERK mitogen-activated protein (MAP) kinase and nuclear factor of activating T cells pathway [38]. Ramar and Caples concluded that vascular changes related to obstructive sleep apnea (OSA) can lead to chronic cardiovascular consequences such as hypertension. The cardiovascular consequences are owing to nocturnal perturbations related to intrathoracic pressure changes, intermittent hypoxia, sympathetic neural activation, endothelial dysfunction, oxidative stress and systemic inflammation. Intermittent hypoxia due to sleep-related events in OSA activates the renin-angiotensin system and increases the levels of endothelin-1. Intermittent hypoxia also results in oxidative stress, as evidenced by elevated levels of xanthine oxidoreductase, lipid peroxidation and the presence of reactive oxygen species. There is also evidence for a decrease in antioxidant capacity. OSA is a state of inflammation as evidenced by elevated levels of C-reactive protein, IL-6, NF-κB, TNF-α, ICAM-1, VCAM-1 and E-selectin. This may suggest that OSA is a predisposing factor for atherogenesis [39]. Cherneva1 et al. found that serum level of resistin is more in OSA patients with impaired systolic function as compared to OSA patients with preserved ejection fraction [40]. Papadopoulos DP found that patients with masked hypertension have lower adiponectin levels and higher resistin levels compared with normotensive individuals [41]. Reilly et al. found that resistin levels were positively associated with levels of inflammatory markers, including soluble tumor necrosis factor-alpha receptor-2, interleukin-6, and lipoprotein-associated phospholipase A2, but not measures of insulin resistance and also were associated with increasing coronary artery calcification (CAC) [42]. Pischon concluded that plasma resistin levels are significantly associated with the presence of CHD in women and this association can largely be explained by concomitant inflammatory processes [43]. Frankel et al. concluded that increased circulating concentrations of resistin were associated with incident heart failure [44]. Lp

Table 4 Mean and standard deviation of blood glucose level in subgroup IIC.

	Minimum	Maximum	Mean	Std. deviation
Fasting serum glucose level	126.00	173.00	149.7179	15.37077
Postprandial serum glucose level	200.00	256.00	224.4359	15.55939

Table 5 Clinical criteria of subgroup IIC.

		Frequency	Percent
Polyurea	+ve	31	77.5
Polydypsia	+ve	31	77.5

Table 6 Mean, standard deviation of eGFR in subgroup IID.

	Minimum	Maximum	Mean	Std. deviation
eGFR	62.80	84.20	77.746	6.587

Table 7 Clinical criteria of subgroup IID.

		Frequency	Percent
Puffy eye lid	+ve	9	69.0
Decreased appetite	+ve	12	92.0
Tiredness or fatigue	+ve	12	92.0
Mid-back pain	+ve	6	46.0
Decreased amount of urine	+ve	7	54.0
Maldigestion	+ve	9	69.0

et al. and Punjabi provide compelling evidence of an independent association between OSA and insulin resistance. This association is present even in non- obese sleep apnea sufferers.

Table 10 Correlation between plasma resistin level and AHI, BMI and SaO_2 in group II.

	Plasma resistin level	
	r	*P*
AHI	0.909	0.001
BMI	0.155	0.117
SaO_2	0.863	0.001

These studies involved larger numbers of subjects than previous studies which failed to show any such association and it may be that these earlier studies were underpowered to show such an association [13,7]. Habib concluded that type 2 DM patients have significantly higher resistin levels that are positively correlated with body fat mass supporting the evidence that resistin plays an important role in the pathogenesis of obesity and insulin resistance [45]. Yin et al. have demonstrated the presence of resistin in saliva of T2DM and non-diabetic subjects. Saliva resistin levels of T2DM are significantly higher than those of non-diabetic controls and found that positive correlation of serum and salivary resistin with BMI and HOMA-IR existed in T2DM [46]. In contrast, Zhang confirmed that resistin levels were the same in diabetic patients as compared to control group [47]. Agrawal et al. found that, in obese adults, increasing severity of OSA is associated with higher serum creatinine levels but not a greater degree of albuminuria [48]. Early studies of OSA and renal function

Table 8 Mean, standard deviation and statistical analysis of AHI, ESS, SaO_2, BMI and plasma resistin level in group II (A, B, C and D).

		Group A	Group B	Group C	Group D	*F* test	*P* value
AHI	Range	10.9–25.9	22.4–45.7	21.5–47.2	21.1–45.2	32.202	0.001
	Mean ± SD	18.68 ± 4.9	31.15 ± 6.27	34.38 ± 8.39	29.22 ± 7.47		
ESS	Range	11–15	11–22	11–23	11–24	9.390	0.001
	Mean ± SD	12.79 ± 1.20	14.47 ± 3.92	17.0 ± 3.83	15.46 ± 4.81		
SaO_2	Range	5.1–14.9	10.3–42.5	12.7–45.6	12.0–43.8	28.016	0.001
	Mean + SD	9.55 ± 2.54	29.90 ± 10.59	27.45 ± 11.55	22.86 ± 11.46		
BMI	Range	25.1–29.3	25.0–34.0	25.0–33.1	25.2–32.8	1.872	0.139
	Mean + SD	27.11 ± 1.30	28.59 ± 2.98	28.01 ± 2.60	27.53 ± 2.24		
Plasma resistin level	Range	15.7–25.3	23.2–30.6	24.5–31.9	22.5–31.8	99.114	0.001
	Mean + SD	18.38 ± 2.62	27.02 ± 2.16	28.34 ± 2.16	26.91 ± 3.19		

Table 9 Mean, standard deviation and statistical analysis of ESS and plasma resistin level in groups I and II (A, B, C and D).

		Group I	Group II A	Group II B	Group II C	Group II D	*F* test	*P* value
ESS	Range	0–6	11–15	11–22	11–23	11–24	45.691	0.001
	Mean ± SD	1.4 ± 2.27	12.79 ± 1.20	14.47 ± 3.92	17.0 ± 3.83	15.46 ± 4.81		
Plasma resistin level	Range	5.6–8.3	15.7–25.3	23.2–30.6	24.5–31.9	22.5–31.8	214.864	0.001
	Mean ± SD	7.12 ± 0.98	18.38 ± 2.62	27.02 ± 2.16	28.34 ± 2.16	26.91 ± 3.19		

demonstrated greater urine protein excretion in the presence of OSA [49,50] that was shown to improve with surgical correction of OSA [51]. Cross-sectional studies found weak associations of proteinuria with arousal index (frequency of arousals during sleep) [52] and minimal oxygen saturation during sleep [53]. Presence of proteinuria represents established glomerular damage [54]. Axelsson found that serum level of resistin was markedly elevated in the CKD patients with both advanced and mild to moderate renal function impairment, as compared to controls and also its level was strongly associated with both GFR and inflammatory biomarkers in CKD. As the significant relationship between plasma resistin levels and insulin resistance was lost following the correction for GFR, resistin is not a likely mediator of insulin resistance in patients with CKD. OSA is associated with hypoxemia and sleep fragmentation, which activates the sympathetic nervous system, the renin-angiotensin-aldosterone system, alters cardiovascular hemodynamics, and results in free radical generation. In turn, a variety of deleterious processes such as endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis are triggered, predisposing individuals to adverse cardiovascular events and likely renal damage. Independent of obesity, OSA is associated with glomerular hyperfiltration and may be an independent predictor of proteinuria, a risk factor for CKD progression. OSA is also associated with hypertension, another important risk factor for CKD progression, particularly protein uric CKD [23].

Conclusions

OSA patients can be complicated with cardiac diseases, DM and renal impairment through elevated resistin serum levels.

Recommendations

Effect of CPAP on resistin serum level must be evaluated in these patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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